Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Product Safety, Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Deputy Director, DE, OBE, CBER
From:	Ohenewaa Ahima, MD Medical Officer, Pharmacovigilance Branch, DE, OBE, CBER
Subject:	Safety and Utilization Review for the Pediatric Advisory Committee
Applicant:	Grifols
Product:	GAMUNEX-C (Immune Globulin Injection (Human), 10%, Caprylate/Chromatography Purified)
STN:	125046/1709
Indication:	For use in Primary Humoral Immunodeficiency (PI), Idiopathic Thrombocytopenic Purpura (ITP) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Meeting Date:	Pediatric Advisory Committee Meeting, April 28-29, 2020

Contents

1 INTRODUCTION

1.1 Objective

This memorandum for the Pediatric Advisory Committee (PAC) presents a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review is the December 4, 2015 approval of the GAMUNEX-C efficacy supplement (STN 125046/1325) to expand the indication to include subcutaneous administration in pediatric patients (ages 2 to 16 years) with primary humoral immunodeficiency.

This memorandum documents the Food and Drug Administration's (FDA's) complete evaluation, including review of adverse event (AE) reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

GAMUNEX-C [Immune Globulin (Human), 10% Caprylate/Chromatography Purified] is a sterile solution of human immune globulin protein. Also present are trace levels of fragments, IgA and IgM. The distribution of IgG subclasses is similar to that found in normal serum. The solution contains no preservatives and is latex-free. GAMUNEX-C is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion exchange chromatography. In the U.S., GAMUNEX-C is approved to be administered intravenously for treatment of Primary Immunodeficiency (PI) in patients 2 years of age or older, Idiopathic Thrombocytopenic Purpura (ITP) in children and adults, and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults. GAMUNEX-C is also approved in the US to be administered subcutaneously for the treatment of PI in patients 2 years of age or older. GAMUNEX-C is supplied in 1 g (10mL), 2.5 g (25 mL), 5 g (50 mL), 10 g (100 mL), 20 g (200 mL), or 40 g (400mL) single use vials. GAMUNEX-C is manufactured in the U.S. by Grifols Therapeutics Inc.

1.3 Regulatory History

- August 27, 2003: Initial U.S. approval of original BLA (STN 125046/0) for intravenous (IV) administration in treatment of PI and ITP.
- September 12, 2008: Approval of efficacy supplement (STN 125046/409) for IV administration in treatment of CIDP.
- October 13, 2010: Approval of efficacy supplement (STN 125046/619) for a new route of administration, subcutaneous (SC) administration, for treatment of PI.

- September 23, 2013: Required safety label change (STN 125046/1198), "…*under Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FDCA)…new safety information pertaining to the risk of thrombosis that we believe should be included in the labeling for the entire class of intravenous, subcutaneous, and intramuscular immune globulin (human) products*."
- December 4, 2015: Approval of efficacy supplement (STN 125046/1325) to expand the indication to include the subcutaneous route of administration in pediatric patients (ages 2 to 16 years) with primary humoral immunodeficiency. **Regulatory trigger for this PAC.**
- September 30, 2019: FDAAA section 921 public posting[1] for the potential signal of serious risk for increased hypersensitivity reactions in patients receiving certain product lots**.**

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
  - FAERS reports for GAMUNEX-C during December 4, 2015 to August 31, 2019 (PAC review period)
- Manufacturer's Submissions
  - GAMUNEX-C U.S. package insert, dated 06/2018
  - Response to information request regarding dose distribution data, received November 19, 2019
  - Pharmacovigilance Plan (Version 4.3), dated November 6, 2019
  - Periodic safety reports
- FDA Documents
  - GAMUNEX-C Approval Letter for STN 125046/1325, dated December 4, 2015
  - Division of Epidemiology Pharmacovigilance Plan Review Memorandum for STN 125046/619, dated April 12, 2010
  - GAMUNEX-C Section 921 Justification Memorandum dated September 25, 2019
- Publications (see Literature Search in Section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for GAMUNEX-C during the PAC review period, December 4, 2015 (PAC trigger) through August 31, 2019 (data lock point for this review).

[1] https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/april-june-2019-potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event

4 PRODUCT UTILIZATION DATA

Grifols provided distribution data for the U.S. and worldwide for time intervals December 4, 2015 to August 31, 2019:

- The total amount of Gamunex-C distributed in the U.S. was (b) (4) grams. Grifols estimates the percentage of use in the U.S. pediatric population to be (b) (4) (for PI, ITP, CIDP, and off-label indications combined)
- Worldwide distribution of Gamunex-C was (b) (4) grams. Grifols estimates the percentage of use in the worldwide pediatric population to be (b) (4) [for PI and secondary immunodeficiencies (including hematopoietic stem cell transplantation and AIDS), ITP, CIDP, Kawasaki disease, Guillain Barre syndrome, and off-label indications[2] combined.]

Grifols based the use of Gamunex-C in the pediatric population on the licensed indications and estimated the percentages from their cumulative pharmacovigilance data.

In their most recent Periodic Update Safety Report (PSUR) covering the period June 1, 2018 to May 31, 2019, Grifols estimates the number of infusions by assuming an average dose of 600 mg/kg body weight and considers (b) (4) kg as the average body weight, which is slightly lower than actual adult weight to account for children. According to Grifols, the usual mean dosage in replacement therapy is 300 mg/kg and in immunomodulation the total dose is 2 g/kg administered in 1 to 5 days. Grifols estimates the total number of infusions using the following equation:

Number of infusions= Commercialized Gamunex-C (g)/(b) (4)

Based on these assumptions, using the distribution data above, a rough estimate of doses would be (b) (4) infusions in the U.S. with an estimated (b) (4) infusions in the U.S. pediatric population. Worldwide the rough estimate of doses would be (b) (4) infusions with an estimated (b) (4) infusions in the worldwide pediatric population. (Since dose is based upon weight, indication, and clinical response, this is only a general estimate. The actual number of doses administered could be substantially lower or higher depending on the amount of product that was distributed but not yet administered, the route used, and the dosage administered).

These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

[2] In their most recent Periodic Update Safety Report (PSUR) for reporting period June 1, 2018 – May 31, 2019, Grifols estimates that off-label use of Gamunex-C accounts for about (b) (4) of all prescriptions. According to Grifols, Gamunex-C is used for numerous off-label indications including neuropathies and dermatological pathologies. The most common off-label indications reported in the most recent PSUR were myasthenia gravis and dermatomyositis.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan (PVP) for GAMUNEX-C is Version 4.3, dated November 6, 2019. Table 1 shows the safety concerns for Gamunex-C. The planned pharmacovigilance action for the important identified risks, important potential risks, and missing information is routine pharmacovigilance activities.

Table 1: GAMUNEX-C Safety Concerns

Important Identified Risks
Hypersensitivity reactions including anaphylactic reactions
Hemolysis
Thromboembolic events
Acute Renal Failure
Aseptic Meningitis
Important Potential Risks
Transfusion Related Acute Lung Injury (TRALI)
Neutropenia
Lupus-like syndrome
Theoretical risk of pathogen infection
Interaction with live attenuated vaccines
Missing Information
Use in women who are pregnant or lactating

Thrombotic events: Prior to this PAC trigger, in 2013, a boxed warning[3] for thrombosis was added to the label of all non-specific immune globulin products, including GAMUNEX-C, as required by FDA. As per FDA safety communication, "*A retrospective analysis of data from a large health claims-related database, as well as continued postmarketing adverse event reports of thrombosis, have strengthened the evidence for an association between the use of intravenous, subcutaneous, and intramuscular human immune globulin products and the risk of thrombosis. This information necessitates a boxed warning for the entire class of products*."[4] The risk of thrombosis was not identified specifically for GAMUNEX-C, and it is considered applicable to all immune globulin products and labeled for this entire product class.

Hypersensitivity reactions: Severe hypersensitivity reactions may occur with IGIV products, including GAMUNEX-C, and "hypersensitivity reactions including anaphylactic reactions" is an important identified risk. Hypersensitivity is a labeled event in sections

[3] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. November 7, 2013. Available at: https://www.gmp-compliance.org/gmp-news/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

[4] FDA Safety Communication: New boxed warning for thrombosis related to human immune globulin products. June 11, 2013. Available at: https://primaryimmune.org/fda-safety-communication-new-boxed-warning-for-thrombosis-related-to-human-immune-globulin-products

5.1 (under Warnings and Precautions) and 6.2 (Postmarketing Experience) of the GAMUNEX-C package insert. Between August 2018 and August 2019, the manufacturer voluntarily recalled five (5) different lots of GAMUNEX-C that were associated with an increased number of hypersensitivity-type reports. On September 30, 2019, in accordance with FDAAA Section 921, FDA posted a potential signal of a serious risk for GAMUNEX-C for "increased hypersensitivity reactions in patients receiving certain product lots." Of note, three additional lots of Gamunex-C have been voluntarily withdrawn by the manufacturer since September 2019 due to an increased number of hypersensitivity-type reports. (Please see section 6.2.3 of memo for additional details.)

Potential risks: The manufacturer added lupus-like syndrome and neutropenia as important potential risks in version 4.0 of the pharmacovigilance plan. The risk of lupus-like syndrome was added in accordance with recommendations by the European Medicines Agency (EMA) in the final assessment report of the signal lupus-like syndrome and related terms with normal human immunoglobulin.

The remaining identified and potential risks for GAMUNEX-C listed in the above table are common to the immune globulin product class and are monitored with routine pharmacovigilance, which includes review of adverse events reports submitted to FDA, manufacturer submitted periodic safety summaries, published literature, and data mining. There are no postmarketing requirement (PMR) safety studies under FDAAA or Risk Evaluation and Mitigation Strategies (REMS).

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of GAMUNEX-C between December 4, 2015 (PAC trigger) to August 31, 2019. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of adverse event (AE) reports for GAMUNEX-C during the PAC review period are listed in Table 2 below. There were 1344 U.S. and 45 foreign reports for review period December 4, 2015 to August 31, 2019. There were 95 reports in pediatric patients.

Table 2: FAERS Reports for GAMUNEX-C during December 4, 2015 to August 31, 2019 (PAC Review Period)

Age	Serious non-fatal, U.S.	Serious Non-fatal, Foreign	Deaths, U.S.	Deaths, Foreign	Non-Serious, U.S.	Non-Serious Foreign	Total, U.S.	Total, Foreign
≤ 16 years	38	3	2	0	52	0	92	3
> 16 years	296	21	10	5	654	0	960	26
Unknown	42	16	3*	0	247	0	292	16
All ages	376	40	15	5	953	0	1344	45

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability or otherwise medically important conditions.
*From the narratives provided, all 3 patients of unknown age were adults.

6.2.1 Deaths

There were 20 deaths following GAMUNEX-C administration during the PAC review period, including 2 pediatric deaths (U.S. reports). All fatal reports were individually reviewed. Pediatric deaths are summarized below.

- Thirteen (13)-year-old male with past medical history of Jacobsen syndrome, hypothyroidism, growth hormone deficiency, antibody deficiency, agenesis of corpus callosum, and tricuspid regurgitation was admitted for multiple strokes 2 days post-GAMUNEX-C infusion. He had a massive stroke two weeks after admission and died one day later. He had been on GAMUNEX-C (35 grams IV every 2 weeks) for approximately 15 months. The time interval between last administration of GAMUNEX-C and death was 17 days. Concomitant medications were levothyroxine, somatropin, and bismuth subsalicylate.
  Indication for use- CIDP.

Reviewer Comment: The patient had multiple comorbidities due to the history of Jacobsen syndrome. Somatropin and GAMUNEX-C may increase a patient's risk for thrombotic events such as strokes. This report did not identify if the patient's stroke was hemorrhagic or thrombotic. The role of GAMUNEX-C, if any, in this patient's strokes and death is confounded by the concomitant use of Somatropin. This patient's underlying conditions, together with the timeline of events (stroke and death 2 weeks after admission and 17 days after last Gamunex-C treatment), suggest etiologies other than Gamunex-C.

- Sixteen (16)-year-old female with past medical history of celiac disease, and common variable immunodeficiency (CVID) experienced sustained seizure and limited brain activity and died sometime after hospital admission. She had been on

GAMUNEX-C (21 grams IV every 4 weeks) for approximately 8 months. The time interval between the last administration of GAMUNEX-C and the onset of seizures and/or death is not known. The report also states that she may have received 1 dose of IVIG but information about the specific brand was not provided. Indication for use- CVID.

Reviewer Comment: There is insufficient information to assess the role of GAMUNEX-C, if any, in this patient's seizure. No additional information was available on the patient's concomitant medications or the time interval between last administration and the onset of seizures.

There were18 adult death reports (13 U.S. and 5 foreign). Cases involved cardiac arrest or myocardial infarction (N = 3); amyotrophic lateral sclerosis (N = 1); acute kidney injury and intestinal infarction (N = 1); lung cancer (N = 1); multiple organ dysfunction syndrome (N = 1). In 9 cases, the cause of death was unknown, or details of death were not reported. Narratives for the remaining cases are provided below:

- Fifty-six (56)-year-old-male with past medical history including immune thrombocytopenic purpura, decreased platelet count, and Parvovirus B19 infection who received GAMUNEX-C while hospitalized and died on the fourth day of infusion. Patient was reported to have fallen that day and was not found for "a while". When he was found he was bleeding from the nose and mouth and was unconscious. Indication for use- Immune thrombocytopenic purpura (ITP).
- Seventy-one (71)-year-old male with past medical history including myasthenia gravis, daily alcohol use, obesity, obstructive sleep apnea, hypothyroidism, hypertension, type 1 diabetes mellitus, and 3rd degree heart block with a pacemaker. Patient was also on daily prednisone. He experienced an anaphylactic reaction during IVIGNex and GAMUNEX-C infusion. Attempts to resuscitate patient were unsuccessful and the cause of death was considered to be related to reaction from IVIG infusion. No further information was available on this case. Indication for use- Myasthenia gravis.

Reviewer comment: This case report is from Canada. IGIVNex is the marketed trade name of GAMUNEX-C in Canada. The manufacturing process for IGIVNex is the same as for GAMUNEX-C but the (b) (4) *plasma is only Canadian. There were no additional reports associated with the Gamunex-C lot associated with this event in the FAERS database.*

6.2.2 Serious Non-fatal Reports

During the PAC review period, there were 416 serious, non-fatal reports; 41 of which involved pediatric patients. The top reported Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs), occurring with a frequency ≥3 reports, for serious non-fatal reports are summarized in Table 3 for pediatric patients. The top reported MedDRA PTs, occurring with a frequency ≥15 reports, for serious non-fatal reports are summarized in Table 4 for adults.

Table 3: Top Preferred Terms (PTs) for pediatric serious non-fatal reports

Preferred Term (PT)	Number of Serious Reports	Label* Status
Urticaria	10	AR
Infusion related reaction	7	Unlabeled
Dyspnoea	6	AR
Rash	6	AR
Hemolytic anemia	5	AR
Headache	5	WP, AR
Hypotension	5	PME
Pyrexia	5	AR
Cough	4	AR
Meningitis aseptic	3	WP, PME
Pruritus	3	Unlabeled
Tachycardia	3	PME
Throat tightness	3	Unlabeled
Wheezing	3	AR

*Label dated 07/2018
PME: Postmarketing experience; WP: Warnings and Precautions; AR: Adverse Reactions; C: Contraindications

Table 4: Top Preferred Terms (PTs) for adult serious non-fatal reports

Preferred Term (PT)	Number of Serious Reports	Label* Status
Urticaria	61	AR
Dyspnoea	46	AR
Infusion-related reaction	42	Unlabeled
Pruritus	40	Unlabeled
Headache	38	WP, AR
Rash	31	AR
Pyrexia	21	AR

Preferred Term (PT)	Number of Serious Reports	Label* Status
Chest discomfort	17	PME
Blood pressure increased	16	AR
Malaise	16	PME
Pulmonary embolism	16	AR
Cough	15	AR
Nausea	15	WP, AR
Vomiting	15	WP, AR

*Label dated 07/2018
PME: Postmarketing experience; WP: Warnings and Precautions; AR: Adverse Reactions; C: Contraindications

Most reported MedDRA PTs for both the pediatric and adult non-fatal serious AEs are labeled events or consistent with an already labeled event. Among the most common pediatric adverse event terms, the PTs infusion-related reaction and throat tightness (both unlabeled) are consistent with the labeled event of hypersensitivity in the Warnings and Precautions as well as Postmarketing Experience sections of the label. The PT pruritus is consistent with itching which is reported in the Adverse Reactions section of the label.

The 41 (38 from the U.S. and 3 foreign) serious non-fatal reports in children included 1 duplicate report. All cases were individually reviewed and did not reveal new safety concerns. The U.S. cases involved prolonged hospitalization for a patient with leukemia (N = 1); hemolytic anemia or hemolysis (N = 6); aseptic meningitis (N = 3). There were twenty-one (21) cases of hypersensitivity-type reaction, 11 of which were associated with 5 withdrawn lots. (Please see additional discussion of withdrawn lots in section 6.2.3).
Remaining cases are summarized below:

- Fifteen (15)-year-old male patient with acute lymphoblastic leukemia (ALL) with immunosuppression who received GAMUNEX-C and experienced Transfusion-Related Acute Lung Injury (TRALI), chronic restrictive lung disease, hyper-eosinophils, and rash. He required intubation and high-dose steroids for treatment of TRALI.
- Six (6)-year-old female patient with nonfamilial hypogammaglobulinemia who received GAMUNEX-C subcutaneously and experienced a necrotic lesion. No further details provided.
- Newborn female patient with severe combined immunodeficiency (SCID) who received GAMUNEX-C and developed high level of CMV antibodies. Mother of patient tested negative for CMV antibodies. The manufacturer did not test

GAMUNEX-C lots for CMV antibodies, however, the reporter attributed the infant's CMV antibodies to GAMUNEX-C. No further details provided.

- Eight (8)-year-old male patient with Kawasaki's disease who received GAMUNEX-C and experienced suspected TRALI. He responded to supportive treatment with oxygen via nasal cannula.
- Sixteen (16)-year-old female patient with autoimmune encephalitis and malignant catatonia who exhibited lack of efficacy during treatment with GAMUNEX-C and multiple other medications.
- Ten (10)-year-old male patient with hypogammaglobulinemia who was treated with GAMUNEX-C and developed a migraine headache requiring hospital admission. He recovered from the event. He subsequently developed migraine headaches again after resuming GAMUNEX-C treatment and was treated in the emergency room. He eventually switched to Gammagard and has not experienced any further reactions.

Reviewer comment: Gammagard Liquid is an IVIG made by a different manufacturer.

Foreign (All from Canada):

- Five (5)-year-old male patient who received GAMUNEX for treatment of sepsis and experienced hypotension, rash, and tachycardia.
- Three (3)-year-old female patient with immune thrombocytopenic purpura (ITP) and hemorrhage who received GAMUNEX, Rituximab, and corticosteroids and experienced treatment failure.
- Seven (7)-year-old female patient with acute lymphoblastic leukemia who received GAMUNEX and experienced increased body temperature, chills, emotional distress, and hypotension.

6.2.3 Increased hypersensitivity reactions in patients receiving certain product lots

Between August 2018 and August 2019, the following five (5) lots were associated with an increased number of hypersensitivity-type reports, which led to voluntary lot withdrawals (Table 5)[5,6,7]. FAERS received a total of one hundred and ninety (190) reports of hypersensitivity-type AEs associated with the 5 withdrawn lots, of which thirteen (13) reports involved pediatric patients. There were no deaths. There were 95 serious non-fatal AEs, including eleven (11) pediatric cases (please see section 6.2.2). Of these eleven (11) pediatric serious adverse events (SAEs), there were 2 cases of anaphylaxis and 2 cases of respiratory distress (no other symptoms reported) and the remaining seven (7) cases involved patients who developed hives. It is important to note

[5] https://www.gamunex-c.com/en/hcp/search?q=lot%20withdrawal
[6] https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_gamunexc_2018-0822.pdf
[7] https://www.asdhealthcare.com/AsdHealthcare/media/AsdLibrary/pdfs/Grifols-Gamunex-C-10-Recall-Customer-Web-Notice-FINAL-12-7-18.pdf

that prior to this, between December 4, 2015 and August 2018, there was on average less than 2-3 hypersensitivity-type AE reports per product lot of Gamunex-C in the FAERS database.

Table 5: Gamunex-C Lots withdrawn between December 4, 2015 – August 31, 2019 (PAC Review Period)

Lot #	Total number of adverse event reports*	Number of pediatric adverse event reports	Date of voluntary withdrawal	Total (g)	Estimated number of infusions**
A1GLB01272	17, including 10 SAEs	1 SAE	16-Aug-2018	(b) (4)	
A4GLC01062	78, including 46 SAEs	10, including 9 SAEs	5-Dec-2018		
A1GLC01372	14, including 3 SAEs	0	21-Feb-2019		
A4GLD00502	41, including 13 SAEs	2, including 1 SAE	28-Jun-2019		
B1GLC01592	40, including 23 SAEs	0	21-Aug-2019		

*The SAEs include the 11 serious non-fatal pediatric reports associated with these withdrawn lots.
**This is an estimated number provided by the sponsor since it is not possible to calculate an exact number of infusions and the dose per patient varies significantly by indication and body weight.

Majority of the events occurred either during infusion of GAMUNEX-C, or within minutes to several hours after the infusion. The SAEs include dyspnea/bronchospasm, laryngeal edema, throat tightness/swelling, lip and/or tongue swelling, airway closure, urticaria, chest pain, increased blood pressure, and angioedema. Patients with SAEs were usually treated with epinephrine, antihistamines, and/or steroids. In some cases, patients were treated in the emergency department and/or hospitalized. On September 30, 2019, the FDA posted a FDAAA section 921 public posting for the potential signal of serious risk for increased hypersensitivity reactions in patients receiving certain product lots**.**

Reviewer comment: *There is variation in clinical practice regarding premedication and the medication(s) used. Certain infusion centers or patients routinely premedicate typically with oral diphenhydramine (dose varies from 12.5 mg to 50 mg) and/or varying dose of an oral steroid. Some centers include acetaminophen in their premedication regimen. Other centers and patients do not routinely premedicate and administer oral*

or IV antihistamines and/or steroids only if a patient experiences a hypersensitivity-type reaction. Therefore, some of the patients who experienced these hypersensitivity-type reactions had received premedication of some kind and others had not.
Of note, since this PAC review period the manufacturer has announced voluntary withdrawals for three (3) additional lots of Gamunex-C:

- *On November 5, 2019 the manufacturer announced a voluntary withdrawal of a 6th Gamunex-C Lot (number A1GLD00622) due to hypersensitivity-type reactions. There are currently twenty-eight (28) adverse event reports, including 3 SAEs, pertaining to this lot in FAERS. One (1) report out of the 28 is a pediatric non-serious AE; there were no pediatric SAEs associated with this lot.*
- *On December 13, 2019 the manufacturer announced a voluntary withdrawal of a 7th Gamunex-C lot (number A4GKD00232) due to hypersensitivity-type reactions. There are currently twenty-two (22) adverse event reports, including 5 SAEs, pertaining to this lot in FAERS. Seven (7) reports out of the 22 are pediatric reports including 4 pediatric SAEs (1 report of anaphylaxis, 2 reports of urticaria and 1 report of rash).*
- *On December 30, 2019 the manufacturer announced a voluntary withdrawal of an 8th Gamunex-C lot (number B3GKD00483) due to hypersensitivity-type reactions. There are currently thirty-one (31) adverse event reports, including 4 SAEs, pertaining to this lot in FAERS. Four (4) reports out of the 31 are pediatric reports including 1 pediatric SAE (upper abdominal pain and urticaria).*

The manufacturer continues to closely monitor reports of hypersensitivity with all product lots to identify any further occurrences. The manufacturer is working with the FDA to evaluate manufacturing processes, donor materials, and other factors that may be contributing to the observed hypersensitivity reactions.

6.2.4 Non-serious Reports

During the reporting period, there were 953 non-serious reports; 52 of which involved pediatric patients all from the U.S. The top PTs occurring with a frequency of ≥3 reports for non-serious reports is shown in Table 6 for pediatric patients. The top PTs occurring with a frequency of ≥20 reports for non-serious reports is shown in Table 7 for adults. Most reported MedDRA PTs are labeled events or consistent with an already labeled event.

Table 6: Top Preferred Terms (PTs) for pediatric non-serious reports

Preferred Term (PT)	**Number of Non-Serious Reports**	Label* Status
Headache	13	WP, AR
Vomiting	10	WP, AR
Rash	9	AR

Preferred Term (PT)	**Number of Non-Serious Reports**	Label* Status
Nausea	6	WP, AR
Fatigue	5	AR
Urticaria	5	AR
Diarrhoea	4	AR
Meningitis aseptic	4	WP, PME
Migraine	4	AR
Pyrexia	4	AR
Cough	3	AR
Infusion related reaction	3	Unlabeled
Pruritus	3	Unlabeled

*Label dated 07/2018
PME: Postmarketing experience; WP: Warnings and Precautions; AR: Adverse Reactions; C: Contraindications

Table 7: Top Preferred Terms (PTs) for adult non-serious reports

Preferred Term (PT)	Number of Non-Serious Reports	Label* Status
Urticaria	152	AR
Pruritus	142	Unlabeled
Headache	140	WP, AR
Rash	118	AR
Nausea	56	WP, AR
Fatigue	49	AR
Dyspnoea	35	AR
Pyrexia	33	AR
Vomiting	33	WP, AR
Erythema	31	AR
Chills	30	AR

Preferred Term (PT)	Number of Non-Serious Reports	Label* Status
Blood pressure increased	29	AR
Influenza-like illness	26	Unlabeled
Malaise	25	PME
Diarrhoea	22	AR
Pain	22	AR
Back pain	21	AR
Dizziness	21	AR
Infusion related reaction	21	Unlabeled
Migraine	21	AR
Myalgia	21	AR

*Label dated 07/2018
PME: Postmarketing experience; WP: Warnings and Precautions; AR: Adverse Reactions; C: Contraindications

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of GAMUNEX-C were disproportionally reported compared to all products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point for the data mining analysis of October 13, 2019. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Product Name (S) run identified a total of 51 preferred terms (PTs) with a disproportional reporting alert. Note that a report may have one or more PTs. (Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean).

<u>PTs related to hypersensitivity reactions:</u>

- Anaphylactic reaction (N = 35); hypersensitivity (N = 63); Rash (N = 227); Urticaria (N = 294); Wheezing (N = 30) are included in C, WP, AR and PME sections. Related PTs include Anaphylactoid reaction (N = 18), infusion site urticaria (N = 6), lip swelling (N = 35), pruritus (N = 253), rash generalized (N = 27), rash pruritic (N = 21), swollen tongue (N = 14), throat tightness (N = 22); Dyspnoea (N = 144; AR).

Reviewer comment: Many of these cases were associated with the increase in hypersensitivity reactions observed from Aug 2018 to AUG 2019, which resulted in

recalled lots and is discussed further in Section 6.2.2. Additionally, all of these PTs are labeled and have been reported and/or observed during clinical trials with IVIG products, even in the absence of the recent lot-associated hypersensitivity issues.

PTs that are labeled and commonly associated with IVIGs:

- Blood pressure increased (N = 76; AR); Chest discomfort (N = 56; PME); Headache (N = 331; WP); Migraine (N =53; AR); Chills (N = 87; AR); Meningitis aseptic (N = 70; WP, PME); Photophobia (N = 16; WP); Transfusion-related acute lung injury (N = 5; WP, PME); Pyrexia (N = 111; AR); Pulmonary embolism (N = 31; WP); Infusion site erythema (N = 7; AR); Infusion site pain (N = 19; AR): Infusion site reaction (N = 16; AR); Infusion site swelling (N = 9; AR); Blister (N = 23) is consistent with bullous dermatitis (PME); Infusion site extravasation (N = 16), Skin mass (N = 7) are consistent with the labeled events local infusion site reaction (AR section).

Reviewer Comment: Pulmonary embolism is a type of thromboembolic event for which there is a boxed warning on all IVIG products.

PTs related to transmission of infectious agents:

- Potential risk of transmission of infectious agents and the passive transfer of antibodies which may confound serologic testing [Antibody test positive (N = 7)], are included in the WP section. Related PTs include; Hepatitis B antibody positive (N = 4); Hepatitis B core antibody positive (N =13); Hepatitis B surface antibody positive (N = 4); Herpes simplex test positive (N = 5); Treponema test positive (N = 4); HTLV-1 test positive (N = 3)

PTs related to hemolysis:

- Hemolysis (N = 54; WP, PME); Haemolytic anaemia (N = 62; AR, PME); Coombs direct test positive (N = 10); Coombs test positive are included in the WP, Clinical Trials Experience, and PME sections. Related PTs include Blood lactate dehydrogenase increased (N = 15), hemoglobinuria (N = 6); hemolytic transfusion reaction (N = 3); Red blood cell spherocytes present (N = 7)

PTs for non-specific unlabeled events: neck pain (N = 27); influenza-like illness (N = 47); Infusion related reaction (N = 135)

PTs that are not adverse events: No reaction on previous exposure to drug (N = 5); incorrect administration rate (N = 5)

PME: Postmarketing experience; WP: Warnings and Precautions; AR: Adverse Reactions; C: Contraindications

Most PTs with an elevated data mining score are already labeled events for GAMUNEX-C and other IVIGs and would be expected to occur more frequently with GAMUNEX-C when compared to all other products in FAERS. All of the PTs identified have had elevated data mining scores previously with GAMUNEX-C, and none are

newly or recently elevated scores. Several PTs were associated with the hypersensitivity reactions recently observed with certain lots and are discussed further in Sections 6.2.2 and 6.2.3. The remaining PTs are associated with hemolysis, or adverse events that would be common during subcutaneous administration (e.g., blisters, infusion site extravasation). There were few of these events relative to the use of GAMUNEX-C.

6.4 Periodic safety reports

The manufacturer's postmarketing periodic safety reports for GAMUNEX-C were reviewed. The adverse events reported were consistent with those seen in FAERS. In the most recent Periodic Safety Update Report covering the period June 1, 2018 to May 31, 2019, the manufacturer reported that a new safety signal had been opened on March 5, 2019 following routine signal detection activities. The signal refers to *increased hypersensitivity/allergic-type reactions* in the U.S. under the *Hypersensitivity Standardized MedDRA Query (SMQ)* with the PTs *lip swelling, pruritus, rash* and *urticaria*. The manufacturer's reason for the evaluation of this signal was based on increased frequency of allergic-type hypersensitivity reactions between December 1, 2018 and January 31, 2019 compared to the previous 2-month period in their safety database. The signal is under further review by the manufacturer including root cause analyses. The increased reports of hypersensitivity reactions recently observed with certain lots are discussed further in Section 6.2.3.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on October 17, 2019, for peer-reviewed literature, with the search term "GAMUNEX-C" and "SAFETY" limited by human species, and dates December 4, 2015 (PAC trigger) to date of search (October 17, 2019), retrieved zero (0) publications pertaining to safety.

8 CONCLUSION

This postmarketing pediatric safety review includes passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for GAMUNEX-C. The PAC review was initiated due to approval of GAMUNEX-C via subcutaneous administration in pediatric patients (ages 2 to 16 years) with primary humoral immunodeficiency. The manufacturer initiated voluntary withdrawal of 5 lots during the PAC review period, and 3 additional lots in November 2019 and December 2019. All the voluntary withdrawals were associated with increased hypersensitivity reactions. On September 30, 2019, FDA communicated this potential signal of a serious risk for hypersensitivity reactions in patients receiving certain product lots in a FDAAA section 921 public posting. FDA is engaged in ongoing discussions with the manufacturer regarding root cause analysis and investigation of implicated lots.

Hypersensitivity reaction is adequately described in the Gamunex-C package insert. FDA will continue to review spontaneous reports of hypersensitivity-type events and conduct lot-specific analysis of adverse event reports as part of continued routine safety monitoring.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of GAMUNEX-C.